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An evaluation of venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine as therapy for acute myeloid leukemia

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Abstract

Introduction: Older patients with acute myeloid leukemia (AML) ineligible for conventional chemotherapy have historically received low-intensity treatments, if any, and have had dismal outcomes. Recent phase III data have demonstrated significant efficacy of venetoclax-based combinations and have begun to address the unmet need in this patient population. As venetoclax-based combinations become increasingly used in the clinical setting, it is important to understand their development, current use, and future directions.

Areas covered: This review covers the clinical development of venetoclax-based combinations for the management of AML, and their current and future use. A search of PubMed and ashpublications.org using the keywords “venetoclax”, “AML”, and “hypomethylating agents” as the search terms was undertaken to identify the most pertinent publications.

Expert opinion: While venetoclax-based combinations have shown excellent responses and improved survival in patients with untreated AML, further studies are required to understand how to expand on their frontline use, manage patients who fail venetoclax-based combinations, and their true efficacy in the relapsed/refractory setting. Management of AML with venetoclax-based combinations is expected to evolve over the next few years.

Keywords

acute myeloid leukemia; AML; azacitidine; cytarabine; decitabine; HMA; hypomethylating agent; LDAC; venetoclax

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Declaration of interest

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1. Introduction

Acute myeloid leukemia (AML) is a heterogenous hematologic malignancy defined by clonal expansion and abnormal differentiation of myeloid progenitor cells of the hematopoietic system [1]. It is a disease with a prevalence of approximately 61,000 in the U.S. and an age-adjusted incidence of 4.3 per 100,000 annually [2]. The median age of diagnosis ranges from 67 to70 years [3]. Standard treatment with curative intent, which includes induction chemotherapy followed by further consolidative chemotherapy, allogeneic hematopoietic cell transplantation (allo-HCT), or both, has led to cure rates of 35–40% in younger patients [4]. Older patients ineligible for induction chemotherapy have not seen the same success rates however. Their response rates and median overall survival (mOS) historically ranged from 11–19% and 5–10 months, respectively [5, 6]. Reasons for this discrepancy include disease-related factors, such as higher rates of unfavorable genetic alterations, and patient-related factors, such as comorbidities that make them less fit for more intensive treatment [7]. As a result, they have historically received low-intensity treatments, such as single-agent therapy with one of the hypomethylating agents (HMA), azacitidine (AZA) or decitabine (DEC), or low-dose cytarabine (LDAC). Some patients received no treatment at all [8]. Thus, there was an unmet medical need for efficacious and tolerable treatments for older, unfit adults with AML.

B-cell lymphoma-2 (BCL-2) is an anti-apoptotic protein that contributes to the survival of AML stem cells and resistance to chemotherapy by binding to proteins that promote apoptosis [9–11]. Venetoclax (VEN) is a selective inhibitor of BCL-2 which showed activity against AML in preclinical studies both alone and as a synergistic agent to AZA [9, 11–13]. Recently, VEN combined with a HMA (HMA-VEN) or LDAC (LDAC-VEN) gained food and drug administration (FDA) approval for patients with newly diagnosed AML ≥75 years of age or who have comorbidities that preclude the use of intensive induction chemotherapy [14]. This accelerated approval was the result of two open-label, non-randomized trials that demonstrated efficacy in the frontline setting [6, 15]. This FDA approval was solidified by a large phase III clinical trial known as the VIALE-A trial that compared AZA plus VEN (AZA-VEN) to AZA plus placebo (AZA-PBO) in untreated older patients with AML [7].

The combination of HMA-VEN for induction in patients with newly diagnosed AML has become widely used due to a favorable safety profile, relative to intensive chemotherapy. Induction HMA-VEN is now considered to be a standard of care for patients unfit for induction chemotherapy due to comorbidities or age, and it may also have a role in r/r disease. Therefore, understanding the efficacy, safety, and tolerability of this combination is critical to help clinicians make informed decisions about treatment selection for AML. In this review, we discuss the clinical development of HMA-VEN and LDAC-VEN for the management of AML and their current and future use.

2. Overview of the market

2.1 What are the unmet needs of currently available therapies?

Selecting the optimal treatment for elderly patients with AML is challenging due to poor performance status and comorbidities, which correlate with a higher incidence of treatment-related complications and early mortality [16, 17]. This has led to a paucity of effective treatments for this group of patients. Further complicating this issue is that no uniform consensus exists for what defines an “unfit” patient, and publications have defined it based on different factors [18, 19]. The VIALE-A trial defined these patients as those ≥ 75 years of age or if they had at least one comorbidity that excluded them form intensive chemotherapy, such as a history of congestive heart failure requiring treatment or an ejection fraction ≤ 50%, chronic stable angina, a diffusing capacity of the lung for carbon monoxide ≤ 65% or a forced expiratory volume in 1 second ≤ 65% and an Eastern Cooperative Oncology Group performance score of 2 or 3. As previously mentioned, less-intensive therapies like LDAC and HMA monotherapy, have often performed sub-optimally in this population while still requiring significant patient effort and participation, such that many patients and providers altogether defer leukemia-directed therapy [20]. These factors emphasize the unmet need for a more efficacious treatment option with a more favorable risk profile for older AML patients unable to undergo intensive chemotherapy.

2.2 Which competitor compounds/classes of compounds are in the clinic/late development?

Alternatives to HMA-VEN or LDAC-VEN in unfit individuals with AML include monotherapy LDAC and HMA as mentioned above. Other alternatives are summarized in Table 1 [21–27].

Investigational agents in development for this particular setting include the anti-CD47 monoclonal antibody magrolimab combined with AZA. It recently showed a CR/CRi rate of 56%, and 67% in those with a TP53 mutation in a phase 1b trial [28]. Expansion cohorts for this study are ongoing (NCT03248479). APR-246, an investigational drug that preferentially induces apoptosis in mutated TP53 AML cells by restoring the wild-type conformation and function of the p53 protein, is currently being studied in combination with AZA in myeloid malignancies (NCT03072043). Preliminary results showed a 50% response rate in 8 evaluable patients with AML with myelodysplasia-related changes (AML-MRC) [29]. Finally, in a randomized phase II study of pevonedistat, small-molecule inhibitor of neural precursor cell expressed, developmentally downregulated protein 8 (NEDD8)-activating enzyme (NAE), combined with AZA vs AZA alone in patients with higher-risk myelodysplastic syndromes/chronic myelomonocytic leukemia and low-blast AML, pevonedistat plus AZA showed a trend towards improved event-free survival (EFS) and OS, and had a similar safety profile to AZA alone [30].

3. Introduction to the drug

3.1 Chemistry

BCL-2 is a family of proteins that regulates mitochondrial outer membrane permeabilization by binding to pro-apoptotic proteins, such as BIM and BAX. BCL-2 homology 3 (BH3) mimetics, such as navitoclax (ABT-737) and VEN (ABT-199), structurally resemble the BH3 domain of sensitizer BH3-only proteins that promote apoptosis and serve as BCL-2 inhibitors that displace BIM and BAX in AML, resulting in irreversible cell death through activation of apoptosis [31]. VEN is a small oral molecule and a potent selective inhibitor of BCL-2, an anti-apoptotic protein that is expressed in over 80% of *de novo* AML cases and up to 100% of cases at relapse [32]. VEN has demonstrated induction of apoptosis in AML myeloblasts as well as leukemia stem/progenitor cells [11]. In a preclinical model, BCL-2 inhibition showed synergistic activity in combination with HMA, specifically by sensitizing AML cell lines to AZA [13]. AZA has also been shown to decrease myeloid cell leukemia-1 (MCL-1) activity, which plays a key role in acquired resistance to VEN [33]. It has been demonstrated that amino acid uptake and metabolism are increased in leukemia stem cells (LSCs) [34]. In particular, LSCs obtained from *de novo* AML patients are especially dependent on amino acid metabolism for oxidative phosphorylation and survival. AZA-VEN can induce LSC death by reducing amino acid uptake. Another analysis of LSCs from patients undergoing AZA-VEN treatment showed disruption of the tricarboxylic acid (TCA) cycle by inhibition of electron transport chain complex II, or succinate dehydrogenase [35]. This suppresses oxidative phosphorylation, which selectively targets LSCs. Thus, one proposed mechanism for the synergistic effects of AZA-VEN is pharmacological inhibition of amino acid metabolism, reducing oxidative phosphorylation and inducing LSC death (Figure 1).

3.2 Pharmacodynamics

Navitoclax was the first developed inhibitor of BCL-2, BCL-X_L, and BCL-w with high affinity ($K_i \leq 1$nM) [36]. Its affinity to BCL-X_L caused dose-limiting thrombocytopenia by directly inducing platelet apoptosis through inhibition of this anti-apoptotic protein [37]. This dose-limiting toxicity ultimately led to the development of VEN, which has five times the affinity to BCL-2 ($K_i < 0.010$ nM) compared to navitoclax and lower affinity to BCL-X_L ($K_i = 48$ nM) [38]. Apoptosis occurs within hours, and dose exposure is correlated with apoptosis [39].

3.3 Pharmacokinetics and metabolism

VEN is available in 10 mg, 50 mg and 100 mg tablets, allowing for careful ramp-up and modification for common drug-drug interactions. VEN is dependent on food for absorption. Specifically, a low-fat meal increases maximum observed concentration (C_{max}) and area under the plasma-concentration time curve (AUC) by 3.4 fold compared to a fasted state and 5.1 fold when taken with a high fat meal. VEN concentration typically peaks about 8 hours after a dose. VEN is highly protein-bound and its apparent volume of distribution ranges from 279 to 411 L [39]. VEN is primarily hepatically metabolized via CYP3A and >99.9% is excreted through the feces [40]. In one pharmacokinetic study, posaconazole, a strong CYP3A4 inhibitor, was estimated to increase VEN C_{max} by 7.1-fold and AUC by 8.8-fold

[41]. Experts have suggested reducing the VEN dose by 75% when combining it with a strong CYP3A4 inhibitor [5].

A phase II trial conducted by Konopleva et al was the first study to show the pharmacologic activity of VEN monotherapy in patients with AML [42]. This study established the recommended dose that served as the basis for future VEN-based combinations tested in subsequent phase I trials. The investigators also examined relatively novel biological correlates like BCL-2, BCL-XL and MCL-1 expression, and BH3 profiling, to predict response to BCL-2 inhibition by VEN. Another interesting discovery was that IDH1/2 mutations served as molecular correlates of sensitivity as 33% of these patients achieved CR/CRi.

4. Clinical Efficacy

4.1 Phase I/II studies

The phase 1b study of HMA-VEN included 145 patients who ≥65 years old with untreated AML and not suitable for intensive chemotherapy [15, 43]. For all phase I-III trials involving HMA-VEN or LDAC-VEN, VEN was ramped up to its target dose over a few days for cycle 1 and started at its target dose for subsequent cycles. All patients received tumor lysis syndrome (TLS) prophylaxis, and posaconazole was used for antifungal prophylaxis in a drug-drug interaction sub-study. The median age was 74 years (range, 65–86), 49% of the patients harbored poor-risk cytogenetics, and 25% had secondary AML. Key results and target dosing are summarized in Table 2. Subgroup analyses for different biological subsets were also performed and are summarized in Table 3. This phase 1b study showed the efficacy and safety of HMA-VEN in unfit AML patients [15]. In a long-term follow-up analysis, 29 and 40 months for patients treated with AZA-VEN and decitabine plus venetoclax (DEC-VEN), respectively, the CR/CRi rates were 71% and 74% [44]. The median DOR was 21.9 months (95% CI, 15.1-30.2) and 15.0 months (95% CI, 7.2–30.0), and the mOS was 16.4 months (95% CI, 11.3-24.5) and 16.2 months (95% CI 9.1-27.8), for AZA-VEN and DEC-VEN, respectively.

The phase Ib/II study for LDAC-VEN included 82 patients ≥60 years with untreated AML and unfit for intense chemotherapy [6]. The median age was 74 years (range, 63–90), 49% had secondary AML, 29% received previous HMA therapy, and 32% had poor-risk cytogenetics. Key results of this study are also summarized in Table 2, while subgroup analyses are summarized in Table 3. Deeper responses were associated with more favorable survival outcomes. No prior HMA exposure, *de novo* AML, and intermediate-risk cytogenetics demonstrated superior survival and response rates.

4.2 Phase III studies

The VIALE-A trial randomized 431 patients, 286 to the AZA-VEN group and 145 to the AZA-placebo (PBO) group, unfit for conventional cytotoxic induction therapy due to comorbidities or an age ≥75 years. (7). Target doses are listed in Table 2. Patients received prophylaxis for TLS and could receive anti-infective prophylaxis.

The median age was 76 years in the two groups (range, 49–91). Secondary AML was present in 25% of the AZA-VEN group and in 24% of the AZA-PBO group, and poor cytogenetic risk was present in 36% and 39%, respectively. The median follow-up was 20.5 months. Key results are summarized in Table 2. AZA-VEN significantly outperformed AZA-PBO, reinforcing this regimens place as a standard of care for unfit patients with newly diagnosed AML. The median time to first response, defined as CR or CRi, was 1.3 months (range, 0.6–9.9) and 2.8 months (range, 0.8–13.2), respectively.

The subgroup analyses are summarized in Table 4. AZA-VEN showed a significantly higher CR/CRi rate than AZA-PBO in patients with IDH1/2, TP53 mutations, and trended towards significance for FLT3 and NPM1 mutated disease. The significance of these analyses show that AZA/VEN has activity in a wide range of biological subsets, including high-risk disease.

The VIALE-C study compared the efficacy and safety of LDAC-VEN to LDAC-PBO in previously untreated patients with AML who were either age ≥75 years or unfit for standard induction chemotherapy [45]. In this study, 143 were randomized to the LDAC-VEN arm, and 68 patients were randomized to the LDAC-PBO arm. Prophylaxis for TLS was provided, as was anti-infective prophylaxis for patients with an absolute neutrophil count below 500/μL.

The median age for all patients was 76 years (range, 36–93). Secondary AML was present in 38% of patients, 32% had poor cytogenetic risk, 20% were previously treated with a HMA, and mutations in TP53, FLT3, IDH1/2, or NPM1 were found in 19%, 18%, 20%, and 15% of patients. The median follow-up time was 12.0 months. Key results of this trial and target doses are summarized in Table 2. The primary endpoint, OS, was not met in this study, but did show a trend towards improved survival in the LDAC-VEN arm. However, after an additional 6 months of follow-up, an unplanned analysis showed a mOS of 8.4 months for the LDAC-VEN arm vs 4.1 months in the LDAC-PBO arm (HR, 0.70; 95% CI, 0.50–0.98; P = .04). The subgroup analyses are summarized in Table 4.

4.3 Safety and tolerability

The safety and AEs of AZA-VEN and LDAC-VEN are described in Table 5. Most non-hematologic AEs with HMA-VEN or LDAC-VEN are typically grade < 3, and are manageable. Conversely, hematologic AEs are frequently grade ≥3 and often require dose reductions or interruptions. In the phase Ib trial by DiNardo et al, there were no dose-limiting toxicities, and no TLS events were reported with HMA-VEN. The 30-day mortality was 3% (5 patients). Forty-six patients (32%) died >30 days after the last administration of the study drug (15). In the VIALE-A trial, TLS occurred during the ramp-up period in 3 patients (1%) in the AZA-VEN group vs 0 patients in the AZA-PBO group. However, all 3 of these cases had transient laboratory changes that resolved with uricosuric agents and calcium supplements without interruption of therapy. The 30-day mortality rates were similar (7% with AZA-VEN, 6% with AZA-PBO) (7).

In the phase Ib/II trial by Wei et al, there were no dose-limiting toxicities in the LDAC plus VEN 600 mg cohort in the dose-escalation phase of the study. TLS (as defined by

laboratory criteria) was reported in 2 patients, but both completed the VEN ramp-up to the targeted dose. Finally, the observed 30-day mortality rate was 6% (n = 5) (6). In the phase III VIALE-C study, the 30-day mortality rate was 13% in the LDAC-VEN group and 16% in the LDAC-PBO group. [45].

5. Post-Marking Surveillance

Recently, three datasets were reported describing the real-world experience managing patients with VEN-based combinations. The AML Real world evidenCe (ARC) Initiative is a multicenter chart review study of adult patients with newly diagnosed AML treated with VEN or non-VEN-based regimens They reported in an interim data analysis that included 33 VEN and 33 control newly diagnosed AML patients CR/CRi/CRh rates of 69.7% and 45.5%, and 1-year OS rates of 67.0% and 44.2%, respectively [46]. In a second analysis utilizing the Flatiron database, 145 AML patients were identified, 61.4% of which received an AZA-based combination [47]. They reported reported a CR/CRh of 63.6%. Finally, a prospective observational nationwide multicenter trial conducted in Israel reported that of the 63 patients that were treated, the CR/CRi rate was 52.3%, and 6 patients went on to receive allo-HCT [48]. AEs regardless of grade were reported in 63.5% of patients, and severe AEs were seen in 41.3% of patients. Febrile neutropenia occurred in 22.2%, and 3.2% experienced grade 2 TLS. The 30-day mortality rate was 6.3%.

6. Regulatory affairs

On November 21, 2018, the FDA granted accelerated approval to VEN plus AZA, DEC, or LDAC for the treatment of newly-diagnosed AML in adults ≥75 years of age, or who have medical conditions that preclude use of intense chemotherapy [6, 43]. On October 16, 2020, the FDA granted regular approval to VEN combined with AZA, DEC, or LDAC for newly-diagnosed AML in adults who are ≥75 years of age, or who have comorbidities precluding intensive induction chemotherapy [7, 45]. The European Medicines Agency authorized the use of AZA for AML that developed from MDS, if the bone marrow contains 20–30% abnormal cells, and AML, where the bone marrow contains >30% abnormal cells [49]. DEC was authorized in the European Union on September 20, 2012 for treatment of adult patients ≥65 years with newly diagnosed *de novo* or secondary AML unsuitable for intense chemotherapy [50]. No European approval exists for VEN for the treatment of AML to date [51]. VEN as part of combination therapy has provisional approval in Australia for the treatment of newly diagnosed adult patients with AML who are ineligible for intensive chemotherapy [52]. VEN-based combinations as first line treatment for AML has been approved in Israel [48]. To the author’s knowledge, this reflects the current approval status of VEN and VEN-based combinations for AML in various countries at the time of this manuscript preparation.

7. Conclusion

Outcomes in elderly patients with AML who are ineligible to receive intensive chemotherapy have historically been suboptimal. The HMA-VEN or LDAC-VEN regimens have now expanded the therapeutic armamentarium in this difficult-to-treat patient

population. These treatments have led to higher remission and survival rates. The successes of HMA-VEN and LDAC-VEN have established these regimens as new standards of care. As more novel and effective treatments for AML arise, further studies will investigate how these newer therapies can be incorporated into these combinations.

8. Expert opinion

Although HMA-VEN and LDAC-VEN have shown promise as first line treatment, further studies are necessary to fully understand their applications and ways to improve these combinations. For instance, modifications, either by introducing targeting or non-targeting agents to the VEN-based combinations, may help to augment the already excellent response rates seen. Additionally, there is currently no standard of care for patients with AML who fail VEN-based therapy, and understanding mechanisms of resistance is crucial. Moreover, the exact role for VEN-based combinations in the r/r setting has not been clearly defined in a randomized study. Finally, there are many practical considerations clinicians need to keep in mind while delivering these therapies, and no unform approach exists to address all of these issues.

8.1 Expanding the frontline use of VEN-based combinations

While HMA-VEN and LDAC-VEN have shown promising results, a number of other approaches with the goal of expanding frontline use and/or improving efficacy of VEN-based combinations are being explored. For instance, it is unclear if younger patients with adverse genetic and molecular features benefit from VEN-based therapies. To address this, one phase I study evaluated a 7-day course of cytarabine with 3 days of anthracycline with VEN and showed a 100% CR/CRi (90% CR) rate in 10 evaluable younger adults age 18–60 years [53]. Another effort to open VEN to the younger population is a phase II trial is currently enrolling patients between the ages of 18–59 with untreated AML (NCT03573024).

A different modification was made in a phase II trial that explored the efficacy and safety of a 10-day DEC course in combination with VEN. The study reported a CR/CRi rate of 61% (95% CI, 54–68) for all patients, 84% (95% CI, 74–91) in newly diagnosed AML, 67% (95% CI, 42–85) in untreated secondary AML, 39% (95% CI, 24–56) in treated secondary AML, and 42% (95% CI, 30–55) in r/r AML [54]. The mOS for each group was 18.1 months (95% CI, 10.0– not reached(NR)) in newly diagnosed AML, 7.8 months (95% CI, 2.9–10.7) in untreated secondary AML, 6.0 months (95% CI, 3.4–13.7) in treated secondary AML, and 7.8 months (95% CI, 5.4–13.3) in r/r AML. Another study with promising results investigated VEN in combination with FLAG-Ida (fludarabine, cytarabine, granulocyte-colony stimulating factor and idarubicin) in both newly diagnosed and r/r AML [55]. They found a CR/CRi rate of 84%, an EFS of 16 months, and an OS that was not reached.

There are also ongoing studies incorporating a molecular-targeting agent with a HMA-VEN backbone (triplet therapy) to further improve patient outcomes in those who harbor specific targetable mutations. These include mutations in IDH1, FLT3, and TP53, or antigen targets such as CD123, which are summarized in Table 6 [56–59]. In the previously mentioned

phase II trial studying a 10-day DEC course with VEN, a subgroup analyses consisting of 14 patients with untreated FLT3-mutated AML and 10 patients who received FLT3 inhibitors, including sorafenib (n=5), gilteritinib (n=4), and midostaurin (n=1), showed a CR/CRi rate of 86% (95% CI, 60–96), and a mOS that was NR (95% CI, 6.6-NR), and a median DOR that was NR (95% CI, 6.4-NR) [54]. This study demonstrated that a triplet therapy with a HMA-VEN backbone may lead to improved responses in a population known to have adverse-risk disease.

There are other ongoing frontline VEN-based combination clinical trials investigating the utility of adding targeting agents or chemotherapy to a HMA-VEN backbone in hopes of further enhancing remission rates, duration, and survival that are summarized in Table 6 [60, 61].

8.2 Relapsed or refractory disease after receiving HMA-VEN or LDAC-VEN

Treatment options for patients ineligible for high-intensity chemotherapy and relapse after treatment with HMA-VEN or LDAC-VEN are limited and have poor outcomes. One study reported a mOS of 2.4 months (range, 0.1–21.2) in 41 patients evaluated and a CR/CRi/MLFS rate of 21% in 24 patients who received salvage therapy after HMA-VEN failure [62].

Currently, one option would be to utilize targeted therapies based on the molecular profile of a patient's AML. For example, targeting FLT3 mutations with sorafenib or gilteritinib, and IDH1/2 mutations with ivosedinib and enasedinib, respectively. For patients with CD33+ r/r AML, GO was shown in a multicenter phase II trial to have an efficacious and safe profile, inducing CR in 26% of patients, a median relapse-free survival of 11 months, and a mOS of 8.4 months [63]. However, it should be noted that the efficacy of these approaches in patients who failed prior VEN-based therapies is unknown since these patients were not the target population for these studies. Finally, one small study did note that responses may be seen in patients who initially respond to HMA-VEN but relapse after therapy interruption [64]. This supports the idea of including prior responders to HMA-VEN in clinical studies that combine novel or targeting agents with a HMA-VEN backbone in r/r AML. If a patient would not be a candidate for any of the therapies mentioned, BSC, which refers to the use of antibiotics, hydroxyurea, hematopoietic growth factors, and blood and platelet transfusions, or even hospice, would be reasonable [65, 66]. Patients who are unable to receive intense chemotherapy and fail VEN-based combinations now represent a major unmet medical need. Clinical trials testing novel agents and drug combinations in this setting are needed and should take high priority. For instance, it has been demonstrated that combining TP53 activation and BCL-2 inhibition overcomes resistance to either independent agent and improves efficacy in preclinical AML models [67]. A small-molecule, APR-246, that reactivates mutant and inactivated TP53 by restoring normal TP53 conformation and function is currently in a phase I trial (NCT04214860).

8.3 Postulated mechanisms of resistance to VEN

One postulated mechanism of resistance is upregulation of the anti-apoptotic protein MCL-1. MCL-1 is thought to become the predominant driver for oxidative phosphorylation

in monocytic LSCs, leading to VEN resistance by evasion of VEN-induced BCL-2 inactivation and reducing mitochondrial stress [68]. A second mechanism is increasing nicotinamide metabolism in relapsed LSCs, thus activating both the metabolism of amino acids and the oxidation of fatty acids to trigger oxidative phosphorylation to allow LSCs to escape the cytotoxic effects of HMA-VEN. Moreover, there may be a selective process of preferential growth of monocytic AML populations, which are resistant to VEN due to loss of BCL-2 expression and dependence on MCL-1 [68–70]. AML with monocytic differentiation did indeed show limited to no response to AZA-VEN in one analysis [68]. Fortunately, an MCL-1 inhibitor, AMG-176, is currently being investigated in a phase I trial (NCT02675452).

Proposed genomic mechanisms of resistance, whether it be primary or acquired, include the birth and/or expansion of a clone harboring mutations that promote AML cell survival [71]. A variety of mutations in different pathways has been described, such as those involved with kinase signaling. These include FLT3-ITD, NRAS and JAK1 mutations. Mutations in U2AF1, U2AF2, SRSF2 and ZRSR2 that lead to alternative RNA splicing have also been reported. Additionally, mutations can occur in cancer-related transcription factors, for instance in IKZF1, SETBP1, RUNX1 and STAT5A. There are also tumor suppressor protein mutations like TP53. Finally, mutations can be seen in epigenetic modifiers, classically BCOR and CREBBP [72]

8.4 HMA-VEN or LDAC-VEN in the relapsed/refractory setting

Several studies have evaluated HMA-VEN in the r/r setting, and have reported a wide range of outcomes. In this setting, CR/CRi rates have ranged from 11.6–62%, while mOS has ranged from 3–7.8 months and in one study was NR. Given the significant variability in response rates and survival among these studies, larger prospective and randomized studies evaluating HMA-VEN in r/r AML are needed. Additionally, a more thorough evaluation of the efficacy in patients with secondary AML or prior HMA treatment is needed. Furthermore, the role of HMA-VEN as a strategy for r/r AML re-induction with goal of bridging to an allo-HCT for consolidation and cure is not well characterized. The largest study addressing this issue is a retrospective study of only 32 patients with AML (19 r/r and 13 de novo) [73]. The investigators concluded that patients in both settings could be successfully bridged to allo-HCT. However, the limited reports available for this strategy include highly varied pre-transplant conditioning strategies and other variables that are difficult to control for retrospectively. Given that the course of allo-HCT can be challenging even for young patients with a good performance status, there may be a role for HMA-VEN in patients with r/r AML as a potentially well-tolerated salvage treatment. Larger prospective and randomized clinical trial data evaluating HMA-VEN for this role will be of significant benefit to the field, although we recognize the challenges with designing such a study given that there is no established standard of care to compare this combination to. One proposed study would be to design a trial for patients with r/r AML who are ineligible for intense chemotherapy and compare LDAC or HMA monotherapy with LDAC-VEN or HMA-VEN, as was done in the VIALE-A and VIALE-C trials in the frontline setting. Another approach would be for unfit patients with r/r AML and targetable mutations, to consider comparing HMA or LDAC plus VEN plus a targeting agent to the targeting agent alone.

8.5 Challenges with HMA-VEN use

Given the novelty of this regimen, different opinions still exist on various practical aspects of this therapy. For instance, if this combination needs to be administered in an inpatient setting, if a ramp-up dose is needed, if antifungal prophylaxis is required and the preferred agent if necessary, if a bone marrow biopsy for response assessment needs to be performed after cycle 1 or if it can be delayed until after 2 cycles, what the optimal duration of therapy is, and how many courses can be given before determining the patient has truly HMA-VEN refractory disease [5, 19, 74, 75]. The National Comprehensive Cancer Institute and FDA provide some recommendations on some of these issues, such as a ramp-up schedule for VEN, obtaining a bone marrow biopsy after the first cycle, and continuing therapy until unacceptable toxicity or progression [14, 76].

Finally, it is worth noting that to date, there are no studies that directly compare AZA, DEC, and LDAC in combination with VEN for newly diagnosed AML. Which agent to use with VEN is ultimately left to the clinician based on their experience or institution availability. We prefer to use AZA-VEN since the efficacy was confirmed with this regimen specifically in the VIALE-A trial. Furthermore, this specific combination showed anti-LSC activity in pre-clinical studies [35]. However, based on the patient's preferences and other clinical factors, we may opt to use DEC-VEN as both HMA-VEN combinations showed comparable efficacy in the phase 1b study. Others have reported a preference for DEC in proliferative disease as would be indicated by leukocytosis on diagnosis (white blood cell count > 10×10^9) as DEC is thought to be more cytotoxic [19]. As for whether the duration of DEC should be 5 days or 10 days, the 10-day regimen has shown promising results in the phase II trial and would be a reasonable option in high-risk biological subsets, but its role for this use still needs to be further clarified, ideally in the setting of a randomized, prospective trial.

It is also worth noting that one of the major challenges with HMA-VEN is the ongoing myelosuppression that occurs even after a patient achieves remission. Indeed, a recent analysis of the VIALE-A showed that many responders to AZA-VEN required a dose modification, whether that be an in-cycle dose interruption, post-remission cycle delay, a reduced VEN dosing days in a subsequent cycle and/or cycle delays [77]. While there is a lack of a standardized approach to managing these complications, it would be reasonable to administer VEN at its target dose until a response is seen and even when a reduction is required after achieving remission, a duration reduction (e.g., 28 days to 21 days) would be preferred over a dose reduction. A 14 day break in between treatment cycles to allow for count recovery would also be acceptable.

There is great potential for the current FDA-approved VEN-based combinations to evolve over the next five years. For instance, the frontline use of these regimens may have broader applicability to the younger population, or they may be combined with targeting or non-targeting agents to further improve their demonstrated efficacy. While treatment options for patients with AML who fail VEN-based combinations remains an unmet need, there are opportunities to elucidate the mechanisms of resistance and discover investigational drugs to combat this resistance. Additionally, while retrospective data support the use of HMA-VEN in r/r AML, randomized trials may better establish its role in this setting. Finally, a study investigating the safety and efficacy of AZA-VEN in the post-allo-HCT setting is currently

underway, which may change the current standard of care for AML in this setting 5-years from now (NCT04161885).

10. Information Resources

The FDA labels for VEN, AZA, and DEC offer clinicians useful information on how to apply these drugs [14, 78, 79]. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology provides evidence-based management guidelines to help clinicians deliver preventive, diagnostic, therapeutic, and supportive services for optimal patient outcomes [76]. The European Leukemia Network (ELN) website also provides information for physicians, researchers, and the public on AML, ongoing clinical trials, research projects, and organizational matters [80]. Finally, a number of reviews describe management strategies for delivering HMA-VEN based on evidence and experience [5, 74, 75].

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Article highlights

- Patients with AML ineligible for intense treatments have historically had poor outcomes due to limited and ineffective treatment options
- HMA-VEN demonstrated excellent response and survival rates and was tolerable in the VIALE-A trial and is now an acceptable treatment option for elderly and unfit patients
- Post-marketing studies continue to show high response rates and promising efficacy with HMA-VEN in patients with AML
- Current strategies to improve the use of VEN-based combinations in the frontline setting are under investigation, including expanding their use to younger AML patients and incorporating them as a backbone for triplet regimens
- AML treatment for patients unfit for intensive chemotherapy who fail VEN-based combinations remains a major unmet medical need that warrants new, effective, and tolerable agents and combinations
- Retrospective data suggest potential efficacy for HMA-VEN in the r/r setting, but larger prospective and randomized studies can help define the role of this combination in r/r AML

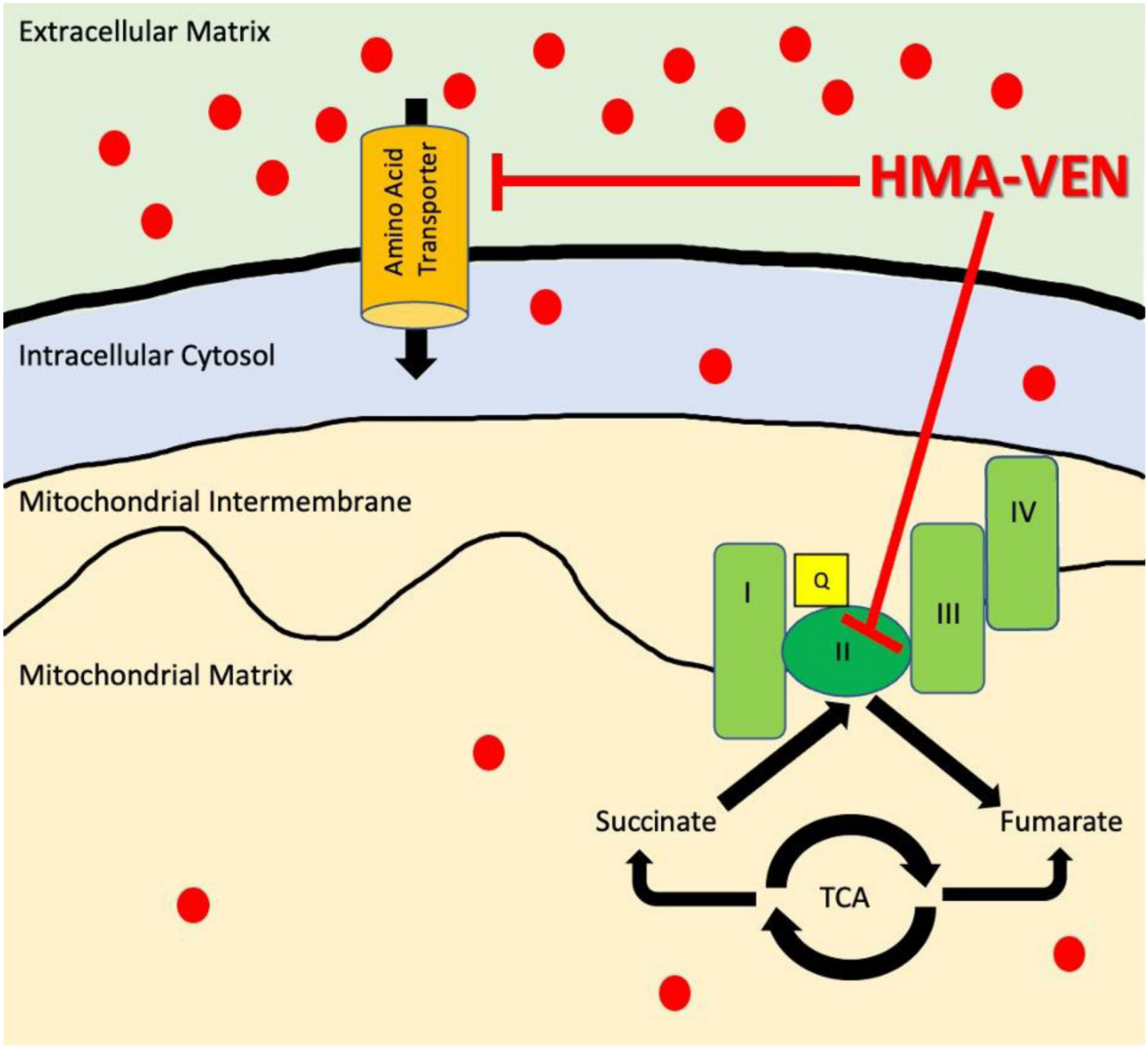

Figure 1:

HMA-VEN demonstrates synergistic activity against leukemic stem cells by inhibiting amino acid uptake and disrupting the tricarboxylic acid (TCA) cycle via inhibition of electron transport chain complex II, ultimately leading to cell death. Amino acids are represented in red circles.

Table 1:

HMA or LDAC plus VEN alternatives

Regimen	Phase	Disease	mOS (95% CI)*	Response rate	Reference
LDAC/glasdegib	II	Newly diagnosed AML/MDS	Glasdegib/LDAC 8.8 months (80% CI, 6.9–9.9); LDAC 4.9 months (80% CI, 3.5–6.0)	CR/CRi/MLFS for AML: 26.9% with glasdegib/LDAC; 5.3% with LDAC	21
Gemtuzumab ozogamicin (GO)	III	Newly diagnosed CD33+ AML	GO 4.9 months (4.2–6.8); best supportive care 3.6 months (2.6–4.2)	CR/CRi rate: GO 24.3%	22
AZA/Midostaurin	I/II	Newly diagnosed and r/r AML/MDS	22 weeks (15–29)	ORR 26%; CR 2%	23
AZA/Sorafenib	II	R/R mutated and wild-type FLT3 AML	All pts: 6.2 months; responders: 7.8 months; nonresponders 6.0 months (P = .01)	CR/CRi 43%	24
Gilteritinib	III	R/R FL3-mutated AML	Gilteritinib 9.3 months; chemotherapy 5.6 months (P<0.001)	CR/CRp: gilteritinib 34.0%; chemotherapy 15.3%	25
Enasidenib	I/II	R/R IDH2 mutated AML	9.3 months for r/r AML, 19.7 months for those achieving CR	CR 40.3%	26
Ivosidenib	I	R/R IDH1 mutated AML	8.8 months (6.7–10.2)	CR/CRp 30.4%	27

*Unless otherwise specified

Table 2:

Summary table of completed trials with HMA-VEN

Trial	Phase	Patient Population	Cohort	n	CR/CRi rate (%)	CR rate (%)	DOR, months (95% CI)	mOS, months (95% CI)	Reference
NCT02203773	1b	Treatment-naïve AML ineligble for intensive chemotherapy	All patients	145	67	37.0	11.3 (8.9-NR)	17.5 (12.3-NR)	15
			DEC 20mg/m2 IV on D1–5 or AZA 75mg/m2 IV or SQ on D1–7 plus VEN 400mg	60	73	Not reported	12.5 (7.5-NR)	NR (11.0-NR)	
			DEC 20mg/m2 IV on D1–5 or AZA 75mg/m2 IV or SQ on D1–7 plus VEN 800mg	74	65	Not reported	11.0 (6.5–12.9)	17.5 (10.3-NR)	
NCT02287233	Ib/II	Treatment-naïve AML ineligble for intensive chemotherapy	LDAC 20mg/m2 daily SQ on days 1–10 plus VEN 600mg po daily	82	54	26	8.1 (5.3–14.9)	10.1 (5.7–14.2)	6
NCT02993523 (VIALE-A)	III	Treatment-naïve AML ineligble for intensive chemotherapy	AZA 75mg/m2 on D1–7 plus VEN 400mg daily	286	66.4	36.7	17.5 (13.6-NR)	14.7 (11.9–18.7)	7
			AZA 75mg/m2 on D1–7 plus PBO daily	145	28.3	17.9	13.4 (5.8–15.5)	9.6 (7.4– 12.7)	
NCT03069352 (VIALE-C)	III	Treatment-naïve AML ineligble for intensive chemotherapy	LDAC 20 mg/m2 plus VEN 600 mg daily	143	48	27	Not Reported *	7.2 (5.6–10.1)	45
			LDAC 20 mg/m2 plus PBO daily	68	13	7	Not Reported *	4.1 (3.1–8.8)	

* Event Free Survival (EFS): 4.7 months (3.7–6.4) LDAC-VEN, 2.0 months (1.6–3.1) LDAC-PBO

Table 3:

Subgroup analyses for phase I/II trials

Trial	NCT02203773			NCT02287233		
Cohort	**HMA-VEN, all patients**			**LDAC 600 mg plus VEN**		
Efficacy	**CR/CRi rate (%)**	**DOR, months (95% CI)**	**mOS, months (95% CI)**	**CR/CRi rate (%)**	**DOR, months (95% CI)**	**mOS, months (95% CI)**
Subgroup						
Cytogenetics						
Intermediate-risk	74	12.9 (11.0-NR)	NR (17.5-NR)	63	Not reported	15.7 (7.0-NR)
Poor-risk	60	6.7 (4.1–9.4)	9.6 (7.2–12.4)	42		4.8 (2.9–11.7)
Age						
≥75 y	65	9.2 (6.4–12.5)	11 (9.3-NR)	60	Not reported	14.9 (6.1-NR)
<75 y	69	12.9 (9.2-NR)	17.7 (14.2-NR)	48		6.5 (11.7-NR)
AML origin						
De novo	67	9.4 (7.2–11.7)	12.5 (10.3–24.4)	71	Not reported	16.9 (11.7-NR)
Secondary	67	NR (12.5-NR)	NR (14.6-NR)	35		4.0 (3.0–6.5)
Associated mutations						
FLT3	72	11 (6.5-NR)	NR (8-NR)	44	Not reported	5.6 (3.0–14.3)
IDH1/2	71	NR (6.8-NR)	24.4 (12.3-NR)	72		19.4 (5.1-NR)
NPM1	91	NR (6.8-NR)	NR (11-NR)	89		NR (0.5-NR)
TP53	47	5.6 (1.2–9.4)	7.2 (3.7-NR)	30		3.7 (0.3–10.1)
Prior HMA thereapy						
Yes	Not reported	Not reported	Not reported	33	Not reported	4.1 (2.9–10.1)
No				62		13.5 (7.0–18.4)
Reference	15			6		

Table 4:

Subgroup analyses for phase III trials

Trial	VIALE-A			VIALE-C		
Cohort	**AZA-VEN**	**AZA-PBO**		**LDAC-VEN**	**LDAC-PBO**	
Efficacy	**CR/CRi rate (%)**	**CR/CRi rate (%)**	**HR for death (95% CI)**	**CR/CRi rate (%)**	**CR/CRi rate (%)**	**HR for death in VEN arm**
Cytogenetics						
Intermediate-risk	74.2	31.5	0.57 (0.41–0.79)	56	16	0.57 (0.40–0.82)
Poor-risk	52.9	23.2	0.78 (0.54–1.12)	28	10	
Age						
<75 y	62.5	41.4	0.89 (0.59–1.33)	44	14	0.56 (0.37–0.84)
≥75 y	69.0	19.5	0.54 (0.39–0.73)	50	13	
AML origin						
De novo	66.4	30.0	0.67 (0.51–0.90)	55	18	0.59 (0.41–0.85)
Secondary	66.7	22.9	0.56 (0.35–0.91)	36	4	
Associated mutations						
FLT3	72.4	36.4	0.66 (0.35–1.26)	45	44	1.11 (0.41–3.0)
IDH1/2	75.4	10.7	0.34 (0.20–0.60)	57	33	0.72 (0.30–1.8)
NPM1	66.7	23.5	0.73 (0.36–1.51)	78	57	0.46 (0.14–1.5)
TP53	55.3	0	0.76 (0.40–1.45)	18	0	0.55 (0.24–1.3)
Prior HMA therapy						
Yes	Not reported	Not reported	Not reported	25	7	0.82 (0.39–1.7)
No				53	15	0.73 (0.49–1.1)
Reference	7			45		

Table 5:

Main adverse events with HMA-VEN and LDAC-VEN

Adverse Event	Trial	
	VIALE-A	VIALE-C
Combination	**AZA-VEN, n (%)**	**LDAC-VEN, n (%)**
Hematologic (grade ≥3)		
Thrombocytopenia	126 (45)	64 (45)
Neutropenia	119 (42)	66 (46)
Febrile neutropenia	118 (42)	45 (32)
Anemia	74 (26)	36 (25)
Non-hematologic (any grade)		
Nausea	124 (44)	60 (42)
Vomiting	84 (30)	36 (25)
Constipation	121 (43)	26 (18)
Diarrhea	117 (41)	40 (28)
Hypokalemia	81 (29)	40 (28)
Peripheral edema	69 (24)	19 (13)
Pneumonia	65 (23)	29 (20)
Serious Adverse Events (any grade)		
Febrile neutropenia	84 (30)	23 (16)
Anemia	14 (5)	4 (3)
Pneumonia	47 (17)	18 (13)
Sepsis	16 (6)	8 (6)
Reference	7	45

Table 6:

Clinical trials expanding the frontline use of VEN-based combinations

Trial	Phase	AML Population*	Modifying intervention	Target of modifying intervention
NCT03404193	II	Newly diagnosed or r/r	10 days of DEC	None
NCT03586609	II	Newly diagnosed	CLAD/LDAC alternating with AZA	None
NCT04435691	Ib/II	Newly diagnosed or r/r	Magrolimab	CD47
NCT04266795	II	Newly diagnosed	Pevonedistat	NAE
NCT04284787	II	Newly diagnosed	Pembrolizumab	PD-1
NCT04150029	II	Newly diagnosed	Sabatolimab	TIM-3
NCT04140487	I/II	Newly diagnosed or r/r FLT3-mutated	Gilteritinib	FLT3
NCT03661307	I/II	Newly diagnosed with poor risk complex karyotype and/or TP53 deletions/mutations or r/r, and detectable FLT3 mutation	Quizartinib	FLT3
NCT03471260	I/II	IDH1-R132 mutated newly diagnosed or r/r	Ivosidenib	IDH1
NCT04214860	I	Mutated TP53	APR-246	TP53
NCT04086264	Ib/II	Newly diagnosed or r/r	IMGN632	CD123

*Pts are not restricted by mutational status unless otherwise stated